What is a truly innovative drug?

New definition from the International Society of Drug Bulletins

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> Growing benefit to patients requires "faster access to increasingly innovative medicinal products whilst guaranteeing a high level of safety," particularly "in the field of biotechnology, gene therapy or pharmacogenomics and xenogenic somatic therapy."[1]

A new creed? No. Claims of drug companies? You are getting warm! Ruthless optimism of this kind is actually widespread among regulatory authorities. Yet according to members of the International Society of Drug Bulletins (ISDB), about 80% of new products or new clinical uses approved each year in developed countries provide no advantage over existing treatments. About 2% of drug treatments offer a real advance to patients, and 5% provide minor benefits. Has this sober picture something to do with the fact that ISDB publications are independent of pharmaceutical companies or that ISDB publications carry comparative information about drugs and therapeutics? The answer is glaringly obvious.

"Innovation" is a strategic concept for all those involved in drug therapy. It is essential for physicians who have an important role in ascertaining the value of a new drug and in deciding whether to prescribe it and for governments and health care providers who decide on and pay for medicines. They have to know whether a so-called innovative product should be covered under provincial drug plans. It is, of course, a strategic concept for drug companies whose innovations are important for their profitability and competitiveness. If we want robust points of reference, patients' needs should come first, and innovation should be defined in terms of comparative advantage over existing treatments.

The experience of ISDB members has shown that the pharmaceutical companies and regulators tend to blur the distinction between genuine therapeutic advance and mere novelty. Pharmaceutical companies increasingly create the impression that it is essential to speed up development and approval of a huge number of "innovative products" so that patients can rapidly have access to them. The gap between regulatory rhetoric and ISDB experience was the driving force behind the *ISDB Declaration on Therapeutic Advance in the Use of Medicines*.[2]

Three concepts of innovation

The term innovation covers three concepts. The commercial concept refers to any *newly marketed* me-too product, new substances, new indications, new formulations, and new treatment methods. The technologic concept means any *industrial innovation*, such as use of biotechnology or introduction of a new delivery system (eg, patch, spray), or selection of an isomer or a metabolite. The concept of *therapeutic advance* is the only one that concerns professionals: it means that a new treatment benefits patients when compared with existing options. It is in pharmaceutical companies' interest to blur the distinction between the three concepts. In the name of claimed innovation and fast-tracking of drug approval, pharmaceutical companies and international pharmaceutical federations have long tried to impose their agenda on regulatory agencies and have in large measure succeeded.

When judging whether a new product is a therapeutic advance, it is crucial to consider efficacy, safety, and convenience. Efficacy, safety, and convenience must be assessed concurrently and regularly re-assessed as new evidence emerges. Indeed, continuous evaluation of old substances is essential so that drugs that are no longer of value can be eliminated, and new or better ways of using already approved drugs can be identified.

Controlled trials are accepted as the standard method for testing efficacy. Their design and performance, however, are often inadequate and lead to unreliable or irrelevant conclusions. Trials often use a wrong reference treatment, which exposes patients to an inadequate level of care

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and is likely to produce results biased in favour of the new drug. When treatment with a favourable benefit-harm ratio is available, placebo-controlled trials on it are ethically unacceptable. Use of clinically irrelevant or methodologically weak outcome measures leads to production of "statistically significant" but meaningless results. Especially controversial and worrying are equivalence trials, which represent a large proportion of industry-sponsored clinical trials. Conducting such trials, often designed for drug registration of me-too products, poses clear ethical problems, because patients in the trials are misled to expect better care.

New drugs are generally approved on the basis of efficacy studies; safety outcomes are considered a secondary issue. Safety concerns include frequent as well as rare and serious adverse effects. At time of first approval, we must be sceptical of the apparently acceptable safety profile of a new drug. Rare adverse effects can be recognized only after a large population has been exposed to the drug. Many regulatory bodies and national and international pharmacovigilance organizations publish little or no safety information for health professionals and the public on the pretext that this information is commercially sensitive.

Pros and cons of convenience

Convenience is helping patients, physicians, nurses, and pharmacists to use drugs well. It includes easy-to-use medications and administration devices, as well as reliable packaging. Greater convenience, resulting in better adherence to a drug regimen, can in itself be an advance. Adherence also depends on the convenience of the administration schedule for patients and health professionals, treatment duration, storage conditions (especially in warmer climates), together with the quality of patient information leaflets. Again we should remain sceptical about claims of greater convenience for drug treatments that are not accompanied by relevant data. But convenience is clearly bad if it leads to overuse or makes harm more likely.

The efficacy of a new drug treatment should be assessed in terms of mortality (where relevant), morbidity, and quality of life from a patient's perspective. Therapies for chronic conditions require long-term trials. Comparative trials assessing the superiority of a drug are needed when an adequately tested treatment is already available. Such requirement is consistent with the latest version of the Declaration of Helsinki,[3] which states that "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods."

Improved safety compared with existing options can qualify a new treatment as an advance provided that short-, medium-, and long-term pharmacovigilance data are taken into account. All information on drug safety (including pharmacovigilance data) should be public from the date of marketing. Most often, several years of active pharmacovigilance are necessary for a new treatment to be accepted as an advance on the grounds of safety. To that effect, health professionals should request from regulatory agencies well-designed pharmacovigilance studies, such as case-control studies and large cohort studies. Without such studies, it is impossible to have a clear picture of safety profiles, including interactions and safety in at-risk groups (such as elderly people, children, pregnant women, and patients with renal failure). Assessment on the safety of prophylactic interventions, such as antihypertensives, requires long-term, large, randomized controlled trials with overall mortality as the main end point. Above all, the benefit-harm ratio of a drug should be critically re-appraised at least every 5 years.

Weakened resistance

Lack of regulatory resistance to pressure from pharmaceutical business has very much weakened the definition of innovation. Regulators should ask pharmaceutical companies for data from comparative evaluations and make them accessible. Without such data, health professionals and the public cannot distinguish useful drug treatments from gimmicks. Regulatory agencies should make available to health professionals and the public a register of clinical trials submitted with applications for drug approval and improve postmarketing surveillance of new drugs.

Governments also have a role, if only to make laws in the interest of public health. They should allocate parts of health care and research budgets to large-scale trials meeting public health needs (drug and nondrug therapies). In particular, adequate public funding is needed for trials unattractive to industry.

Censorship of investigators is a cause for concern. The secrecy clause that prevents them from publishing study results without sponsor approval is an obstacle to honest information and a cause of publication bias. Health professionals on ethics committees should not approve a study protocol

unless it is stated in writing that the full results will be made public as soon as the product is approved for marketing.

Physicians and pharmacists should be able to compare new therapies with existing ones, so that they can identify therapeutic advances reliably. They should be trained to use evidence-based medicine and be able to assess benefit-harm ratios and cost effectiveness. For newly marketed treatments, health professionals should have all the information to explain its advantages and disadvantages in comparison with established treatments. With this information, patients can make informed choices and be aware that any unexpected or unwanted effects should be reported.

Finally, health professionals should be aware that drug information coming from pharmaceutical representatives is not helpful because of lack of comparison with other treatments and of frequently exaggerated claims. Initial and continuing medical education on medicines should be conducted independently of the pharmaceutical industry.

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